

## Supplemental Material\*

Goshua G, Calhoun C, Ito S, et al. Distributional cost-effectiveness of equity-enhancing gene therapy in sickle cell disease in the United States. *Ann Intern Med.* 30 May 2023. [Epub ahead of print]. doi:10.7326/M22-3272

### Contents

Methods .....	2
Distributional cost-effectiveness analysis (DCEA) methods .....	2
Quality-adjusted life years .....	2
Cost modeling and state transition probabilities.....	2
Probabilistic sensitivity analysis .....	3
Supplement Figure 1. Markov trace verification for standard-of-care strategy (SOC).....	4
Supplement Figure 2. Tornado diagram by sex. ....	5
Supplement Table 1. Model verification of gene therapy versus standard-of-care comparison with treatment at age 0 (i.e., at birth) by sex. ....	6
Supplement Table 2. Age-dependent estimates derived from regression for transition probabilities and costs for ages 25, 50, 65 by sex and rounded to two decimal points. ....	7
Supplement Table 3. Scenario analyses.....	9
Supplement Table 4. Base-case results and probabilistic sensitivity analysis by sex. ....	10
References.....	11

\* This supplemental material was provided by the authors to give readers further details on their article. The material was not copyedited.

## **Methods**

### *Distributional cost-effectiveness analysis (DCEA) methods*

DCEA quantifies the distribution of costs and effects of alternative interventions by explicit equity-relevant variables and estimates the trade-offs between efficiency (improving total health under a constrained budget) and equity (improving health inequality) using a welfare function that is determined by an inequality aversion parameter. (1–3) The Atkinson social welfare index is a social welfare function that is commonly used in DCEA (4). The inequality aversion parameter (or equity weight) measures the rate at which society trade-offs total health for health equality. The inequality aversion parameter used to calculate the equally distributed equivalent (EDE) of each intervention. The EDE represents the amount benefits (e.g., health outcomes) in an equally distributed scenario (i.e., all individuals have the same level of overall health) that gives the same amount of welfare as an unequal distribution of benefits. (2, 5) When the inequality aversion parameter is greater than 0, the EDE of an unequal distribution of health is lower than the average level of health in that equal distribution.

### *Quality-adjusted life years*

QALYs are calculated by combining health-related quality-of-life (quantified using different utility values to applied various health states) with the time spent in these health states. Utilities range from 0 to 1 with 0 set for the death state and 1 set for perfect health. In our analyses, utility values were informed by published lifetime simulation of patients living with SCD and matched controls.(6) These were originally derived from a polynomial fit linking the EQ-5D to the visual analog scale for pain in patients with SCD in several studies.(7–9)

### *Cost modeling and state transition probabilities*

We derived the costs from a generalized linear model with Gamma log-link regression coefficients and transition probabilities between disease severity states were derived from

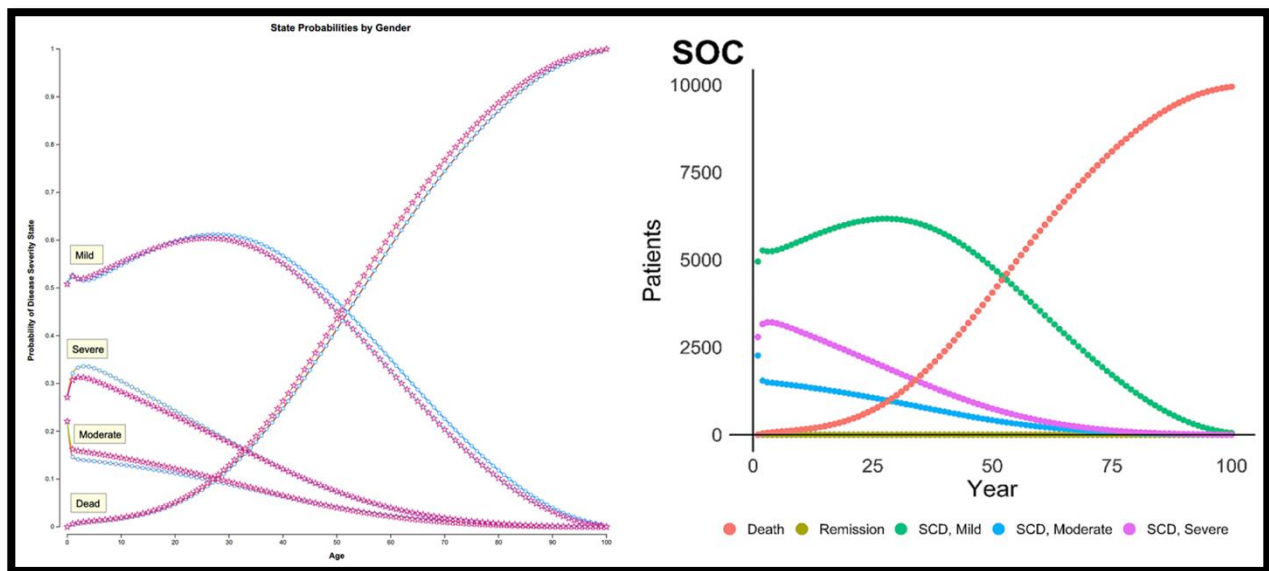
an ordinal logistic regression model reported by Salcedo and colleagues (10). Coefficients in the ordinal logistic regression were originally calculated for each sex by regressing known SCD severity in a given year on SCD severity in the prior year, patient age, and the interaction of severity and age.

#### *Probabilistic sensitivity analysis*

To perform the PSA, we assigned appropriate probability distributions to all input parameters in our model where sampling uncertainty in the underlying data source could be specified (Table 1). For ordered logistic transition probability coefficients and generalized Gamma log-link cost regression coefficients, we used Beta-PERT distributions to approximate prior reported normal distributions, while simultaneously ensuring random draws (10,000 second-order Monte Carlo iterations) from the respective distributions were drawn from 95% uncertainty intervals (10). For utility weights we similarly employed Beta-PERT distributions.

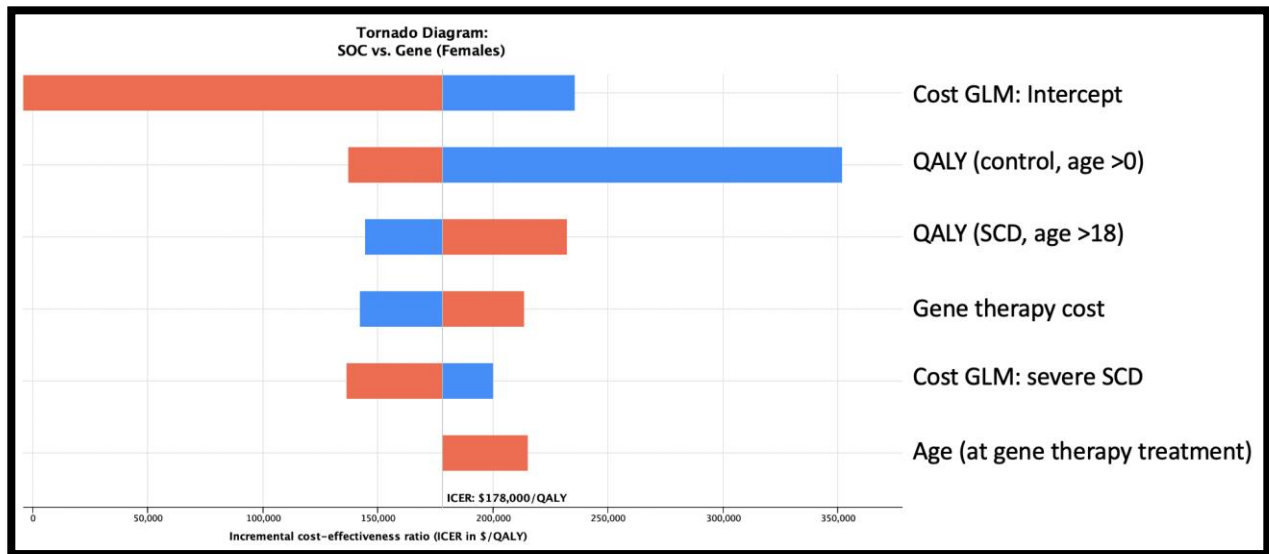
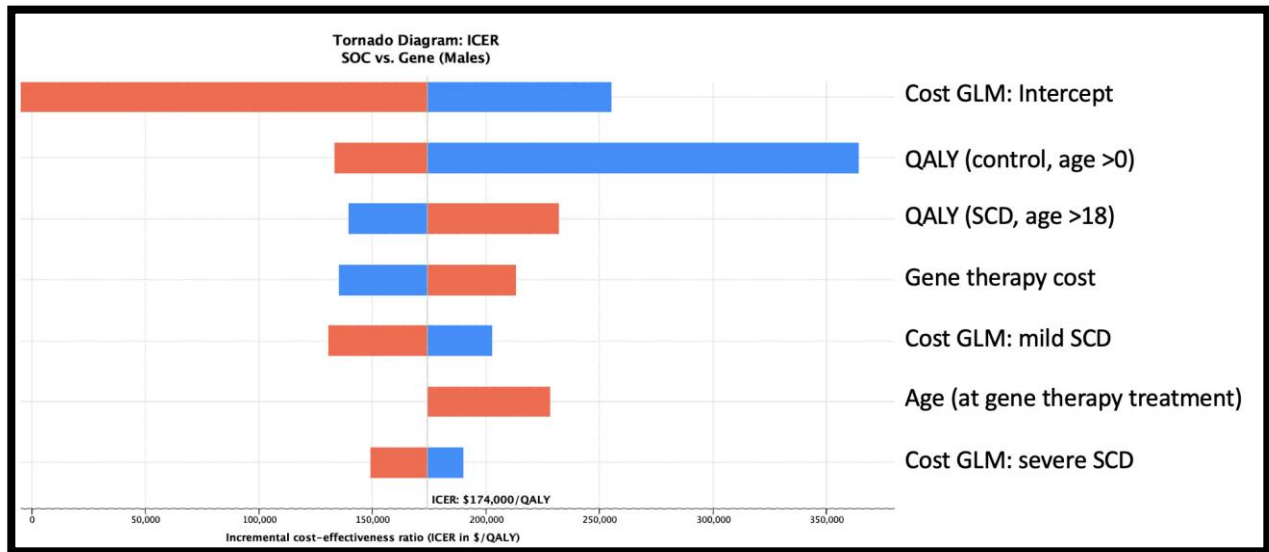
**Supplement Figure 1. Markov trace verification for standard-of-care strategy (SOC).**

Shown are probabilities of being in a mild, moderate, or severe state of sickle cell disease by age for each sex starting at age 0 for cohort of females (blue circles) and males (purple stars) with Salcedo et al.<sup>10</sup> on the right for comparison.



### **Supplement Figure 2. Tornado diagram by sex.**

Parameters affecting incremental cost-effectiveness ratio  $> \pm 10\%$ . GLM = generalized linear model, SCD = sickle cell disease, SOC = standard-of-care



**Supplement Table 1. Model verification of gene therapy versus standard-of-care comparison with treatment at age 0 (i.e., at birth) by sex.**

<b>Treatment strategy</b>	<b>Cost (\$ mil USD)</b>	<b>QALYs</b>	<b>ICER (\$ USD per QALY)</b>	<b>Treatment strategy</b>	<b>Cost (\$ mil USD)</b>	<b>QALYs</b>	<b>ICER (\$ USD per QALY)</b>
<b><i>Salcedo<sup>10</sup>, Females (therapy age 0)</i></b>				<b><i>Salcedo<sup>10</sup>, Males (therapy age 0)</i></b>			
SOC	1,098,098	18.0	--	SOC	1,244,733	17.9	--
Gene therapy	2,377,583	26.8	146,511	Gene therapy	2,367,928	26.1	135,574
<b><i>Goshua, Females (therapy age 0)</i></b>				<b><i>Goshua, Males (therapy age 0)</i></b>			
SOC	1,107,907	18.0		SOC	1,232,027	17.8	
Gene therapy	2,372,193	26.7	145,054	Gene therapy	2,359,407	25.9	139,867

**Supplement Table 2. Age-dependent estimates derived from regression for transition probabilities and costs for ages 25, 50, 65 by sex and rounded to two decimal points.**

<b>Population</b>	<b>Transition probabilities</b>	<b>Costs (Undiscounted)</b>	<b>Source</b>
<i>Females</i>			OptumRx
Age 25			2007-2017 <sup>10</sup>
Mild to Mild/Mod/Severe	0.84/0.08/0.08	\$26,265.20 [Mild]	
Mod to Mild/Mod/Severe	0.61/0.17/0.22	\$29,319.26 [Mod]	
Severe to Mild/Mod/Severe	0.19/0.16/0.66	\$93,060.03 [Severe]	
Age 50			
Mild to Mild/Mod/Severe	0.91/0.05/0.04	\$45,524.23 [Mild]	
Mod to Mild/Mod/Severe	0.71/0.14/0.15	\$45,981.76 [Mod]	
Severe to Mild/Mod/Severe	0.21/0.17/0.63	\$116,541.18 [Severe]	
Age 65			
Mild to Mild/Mod/Severe	0.94/0.03/0.03	\$63,322.75 [Mild]	
Mod to Mild/Mod/Severe	0.77/0.11/0.12	\$60,234.47 [Mod]	
Severe to Mild/Mod/Severe	0.22/0.17/0.61	\$133,385.67 [Severe]	
<i>Males</i>			OptumRx
Age 25			2007-2017 <sup>10</sup>
Mild to Mild/Mod/Severe	0.82/0.09/0.09	\$45,297.18 [Mild]	
Mod to Mild/Mod/Severe	0.63/0.16/0.21	\$29,289.96 [Mod]	
Severe to Mild/Mod/Severe	0.22/0.17/0.62	\$75,659.63 [Severe]	

Age 50			
Mild to Mild/Mod/Severe	0.91/0.05/0.04	\$55,326.10 [Mild]	
Mod to Mild/Mod/Severe	0.73/0.13/0.14	\$62,006.84 [Mod]	
Severe to Mild/Mod/Severe	0.20/0.16/0.64	\$121,661.76 [Severe]	
Age 65			
Mild to Mild/Mod/Severe	0.94/0.03/0.03	\$62,380.00 [Mild]	
Mod to Mild/Mod/Severe	0.78/0.11/0.11	\$97,246.08 [Mod]	
Severe to Mild/Mod/Severe	0.19/0.16/0.65	\$161,781.19 [Severe]	

**Supplement Table 3. Scenario analyses.**

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year, SOC = standard-of-care, USD = United States Dollar

<b>Treatment strategy</b>	<b>Cost* (\$ mil USD)</b>	<b>QALYs*</b>	<b>ICER* (\$ USD per QALY)</b>	<b>95% Credible Interval (ICER) for Females and Males</b>	<b>Threshold Inequality aversion parameter</b>
<b><i>Scenario: Gene therapy durable for 20 years (all patients)</i></b>					
SOC	1,120,000	15.6	--		
Gene therapy	3,100,000	20.1	438,000	[395,000-521,000] and [298,000-554,000]	2.1
<b><i>Scenario: Gene therapy durable for 10 years (all patients)</i></b>					
SOC	1,120,000	15.6	--		
Gene therapy	3,280,000	18.1	855,000	[729,000-1,090,000] and [680,000-1,140,000]	3.0
<b><i>Scenario: 18.9% of all patients with sickle cell disease excluded from gene therapy due to comorbidities** (all patients)</i></b>					
SOC	1,120,000	15.6	--		
Gene therapy	2,500,000	23.3	175,000	--	0.8

\*lifetime, discounted, per-person results for full population

\*\*heart failure or pulmonary hypertension

**Supplement Table 4. Base-case results and probabilistic sensitivity analysis by sex.**

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year, SOC = standard-of-care, USD = United States Dollar

<b>Treatment strategy</b>	<b>Cost* (\$ USD)</b>	<b>QALYs*</b>	<b>ICER (\$ USD per QALY)</b>	<b>95% Credible Interval (ICER)</b>	<b>Threshold inequality aversion parameter (equity weight)</b>
<b><i>Females</i></b>					
SOC	1,040,000	15.7	--		--
Gene therapy	2,790,000	25.5	178,000	[155,000-228,000]	**
<b><i>Males</i></b>					
SOC	1,190,000	15.5	--		--
Gene therapy	2,750,000	24.4	174,000	[14,800-243,000]	**

\*lifetime, discounted, per-person results

\*\*not included (sex-specific threshold inequality aversion parameters not relevant for any policy decisions or model validation)

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